REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Finality of Office Action

Applicant respectfully urges reconsideration and withdrawal of the finality of the Office Action mailed March 11, 2010. Although the MPEP indicates that the first Office Action after an RCE may be made "final" under the circumstances cited in the Office Action, the decision to make the first Office Action after an RCE final is at the ***discretion*** of the examiner. That is, the MPEP provides that "[t]he claims of an application for which a request for continued examination (RCE) has been filed ***may*** be finally rejected in the action immediately subsequent to the filing of the RCE" (emphasis added).

Applicant respectfully urges reconsideration of the finality of the Office Action here because it is contrary to the USPTO goals of compact prosecution. In the previous response, Applicant amended claim 1 to recite a blister pack for pharmaceutical use comprising blisters containing a compressed "granulate" tablet. Applicant made these amendments with an RCE in order to expedite prosecution, *e.g.*, in order to avoid the delays associated with filing an Amendment under 37 CFR § 1.116, receiving an Advisory Action refusing to enter the amendments, and then filing an RCE. (The previously pending claims did not expressly recite "granulate" so Applicant did not believe that the amendments would have been entered after "final.") If Applicant had followed these procedures, which can add ***months*** to the prosecution timeline, the Examiner would not have been permitted to make this Office Action final. As set forth in MPEP § 706.07(b), "it would not be proper to make final a first Office action in . . . an RCE where that application contains material which was presented . . . after final rejection . . . but was denied entry because (A) new issues were raised that required further consideration and/or search, or (B) the issue of new matter was raised." By making this Office Action final, the Examiner in effect is penalizing Applicant for pursuing a prosecution strategy that promoted the USPTO goals of compact prosecution.

Applicant therefore respectfully urges reconsideration and withdrawal of the finality of the Office Action, or at least entry of the amendments submitted herewith.

Claim Amendments

Claim 1 is amended to more directly recite aspects of the claimed subject matter, e.g., to expressly state that the recited compressed granulate tablets comprise a compressed granulate that comprises the recited components (desmopressin or a pharmaceutically acceptable salt thereof, an acid, and a pharmaceutically acceptable adjuvant, diluent or carrier). Applicant believes that the previously pending claims recited this same subject matter and, thus, that the amendment does not raise any new issues or require a further search or consideration.

Claim 18 is added to recite specific embodiments, where the compressed granulate tablet comprises desmopressin acetate. This subject matter is fully encompassed by previous claim 1, which recited a compressed granulate tablet comprising "desmopressin, or a pharmaceutically acceptable salt thereof," because desmopressin acetate is a pharmaceutically acceptable salt of desmopressin, as taught, for example, in paragraph [002] of the application as filed. Accordingly, this claim does not raise any new issues or require a further search or consideration.

Applicant urges entry of these amendments after final, because they do not raise new issues that would require further consideration and/or search, and they do not raise the issue of new matter. Moreover, the amended claims are believed to be in condition for allowance or, at the very least, in better condition for appeal.

After amending the claims as set forth above, claims 1, 3-4, 6-7, and 13-18 will be pending. These claims are presented for reconsideration.

Claim Rejections under 35 U.S.C. §103(a)

Claims 1, 3-7, and 13-17 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Fein (US Publication No. 2004/0138098). Applicant respectfully traverses.

As reflected in independent claim 1, the instant claims are directed to a blister pack for pharmaceutical use comprising blisters containing a compressed granulate tablet which tablet comprises a compressed granulate comprising: desmopressin, or a pharmaceutically acceptable salt thereof; an acid that provides a pH in the range of from 3.0 to 6.2 as measured when 1 g of said tablet is slurried in 2 ml of water at 25°C; and a pharmaceutically acceptable

adjuvant, diluent or carrier. Fein does not teach or suggest a blister pack comprising such compressed granulate tablets.

Fein does not teach compressed granulate tablets

Fein is directed to orodispersible forms of desmopressin which are absorbed directly from the mouth, instead of being swallowed. Fein's tablets are ***not*** compressed granulate tablets as recited in the instant claims, but rather are fast-dissolving tablets formed by direct compression of a mixture of the materials. *See, e.g.* Fein, page 5, paragraphs [0055] – [0058]. Indeed, Fein's goal of rapid dissolution in the mouth is inconsistent with compressed granulate tablets. This is seen in Comparative Examples 2 and 3 of Fein, which describe granulate tablets in ***contrast*** to Fein's tablets. Thus, at its most fundamental level, Fein is not related to the dosage forms recited in the instant claims.

At page 7 of the Office Action, the Examiner "respectfully disagrees" with Applicant's explanation of Fein, alleging that "Fein's tablet is in fact a compressed dosage form wherein particles (e.g. granules) of the active ingredient and a protective material are provided as a hard, compressed tablet for direct oral dosing," citing paragraph [0040] of Fein. This assertion reflects an incomplete understanding of the technology at issue, and a lack of understanding of the specific technical meaning of "compressed granulate" in the field of solid dosage forms.

Granulation is a specific manufacturing process whereby the components are "granulated"—formed into small granules—prior to compression into tablet form. As taught in the application and illustrated in the examples, commercially available tablets of desmopressin are made by a wet granulation process. As illustrated in Example 1, this process entails mixing the components in a granulation liquid, sieving to obtain granulate of a specific size (determined by the sieve size), and drying, all prior to compressing into tablet form.

In contrast, direct compression is a more simple manufacturing process that involves mixing the dry components and then "directly" compressing them into tablet form. *See, e.g.* Fein, page 5, paragraphs [0055] – [0058].

These different manufacturing processes result in products that differ at a ***physical*** level. Compressed granulate tablets are comprised of compressed ***granules***, while directly

compressed tablets simply comprise a compressed form of the original dry component mixture.

When the terminology of the instant claims is properly understood (as it would be by those skilled in the art), it is readily apparent that Fein's directly compressed tablets do not teach, suggest or read on a compressed granulate tablet as recited in the instant claims.

Fein does not teach a compressed granulate comprising desmopressin and an acid

As explained previously, Fein does not teach or suggest the use of an acid in a compressed granulate tablet where the acid provides a pH in the range of from 3.0 to 6.2 when 1 g of the tablet is slurried in 2 ml of water, as recited in the instant claims. The Office Action cites Fein's teaching of the use of an acid source in combination with a carbon dioxide source, such as alkaline carbonate or bicarbonate, to make the effervescent agent that evolves gas (see Fein, page 5, paragraph [0061]), but this teaching does not suggest the use of an acid to provide a pH as claimed. Indeed, Fein teaches the use of an acid source in conjunction with a the carbon dioxide source, preferably in equivalent ratios. *See, e.g.*, Fein, page 5, paragraph [0062]. Slurrying such a tablet in water would promote reaction between the acid and effervescent agent, resulting in consumption of the acid, not the provision of a desired pH, as claimed.

In any event, as the instant claims expressly recite that the claimed compressed granulate tablets comprise a ***compressed granulate*** that comprises both desmopressin (or a pharmaceutically acceptable salt thereof) and an acid, and because Fein does not teach or suggest any compressed granulate products, Fein simply cannot and does not teach or suggest the claimed invention.

Fein does not teach packaging a desmopressin tablet in blister packs

The Office Action disagrees with Applicant's statement that Fein does not teach packaging a compressed granulate tablet of desmopressin in blister packs, but rather discloses blister packaging only in connection with the preparation of a freeze-dried product which is not a compressed tablet of any kind. *See, e.g.*, Fein, page 8, paragraphs [0092] and [0093]. The Examiner's position is based in part on his incomplete understanding of the technology, and the differences between compressed granulate tablets (the invention) and direct

compression tablets (Fein), as explained above. When the claimed subject matter is correctly understood as it would be by the skilled artisan, this aspect of the rejection should be withdrawn.

In maintaining this aspect of the rejection, the Office Action notes that Fein teaches that its formulations "have a sufficient strength for handling, which in practice may mean sufficient strength to withstand removal from a blister packaging without disintegrating," citing Fein, paragraph [0033]. This paragraph of Fein relates to "intrabuccally disintegrating [orodispersible]solid formulations," which are separate and distinct from the "hard, compressed, rapidly dissolving tablet[s]" discussed in paragraph [0040] of Fein. As illustrated in Fein's examples, the orodispersible dosage forms are actually made directly in the blister packages, by pipetting an appropriate amount of liquid pharmaceutical formulation into the blister pockets and freeze drying. *See, e.g.*, Fein paragraph [0119]. In contrast, Fein expressly teaches storing its directly compressed tablets in bulk, *i.e.*, not in a blister pack. *See, e.g.*, Fein, page 3, paragraph [0040].

As explained previously, while the Examiner might assume that any dosage form of desmopressin can be packaged in any manner, such an assumption ignores the state of the art with regard to desmopressin. As set forth in paragraph [0004] of the instant specification, the desmopressin acetate tablet product Minirin® was marketed in a blister pack, but the blister pack product was withdrawn from the market in 2002 due to a consistent problem with degradation of the desmopressin acetate during long term storage. Knowing of this problem, the skilled artisan would have been discouraged from packaging desmopressin ***tablets*** in blister packs, and Fein's teaching to package ***freeze dried*** dosage forms in blister packs would not have convinced them otherwise. Indeed, while Fein emphasizes that orodispersible forms can withstand the ***physical stresses*** of being removed from blister packaging, it does not examine the long-term stability of its products.

The unexpected results pertain to the claimed invention

As set forth in Applicant's previous response, the present invention advanced the state of the art by providing a form of desmopressin that can be packaged in blister packs without suffering from degradation. As taught in the specification, it was surprisingly discovered that the claimed compressed granulate tablets show unexpected stability when stored in blister

packs. For example, paragraph [0011] teaches that "it has been found that a purposive selection and control of the pH level in a solid dosage form of desmopressin is particularly efficient in counteracting degradation upon storage in blister packs." The unexpected results are illustrated, for example, in Example 3 (PVC blister) and Example 4 (PVC/PVDC blister) at pages 7-8 of the specification, which compare the degradation of desmopressin (upon storage) with respect to compressed granulate tablets with and without an acid as recited in the pending claims. Example 3 demonstrates that the tablet with acid retains 76% of its desmopressin after 7 months of storage as compared to only 52% remaining in the tablet with no acid. Similarly, Example 4 demonstrates that the tablet with acid retains 82% of its desmopressin after 6 months of storage as compared to 76% of desmopressin in the tablet with no acid. Thus, the present invention solves a significant problem faced by the art, and provides a solution that is not taught or suggested by Fein.

At page 9, the Office Action dismisses this evidence, drawing a line between "desmopressin" and "desmopressin acetate." Such a line does not exist in the pending claims, however. Claim 1 consistently has recited "desmopressin, or a pharmaceutically acceptable salt thereof," which includes desmopressin acetate. To underscore this point, Applicant has added claim 18, which expressly recites the pharmaceutically acceptable salt desmopressin acetate.

Perhaps more importantly, there is no basis in the record for the assertion implied in the Office Action that the stability problems observed with the commercial tablet of desmopressin is due to its being an acetate salt, or for the assumption that the problem could have been solved by using desmopressin in its free base form. To the contrary, as taught in paragraph [0010] of the instant specification "the inventors hypothesise [without being bound by a particular theory], that the presence of ***residual moisture*** in solid dosage forms of desmopressin in combination with the increased potential influx of moisture in blister packs (compared e.g. to sealed bottles) caused the aforementioned accelerated ***degradation of desmopressin*** upon storage," and that "[t]he presence of moisture in solid dosage forms appears to promote ***dimer formation . . .*** of ***desmopressin***" (emphasis added).

Thus, the unexpected results reported in the specification support the nonobviousness of the full scope of the claimed invention, and are not diminished by the teachings of Fein.

In view of the foregoing, Applicant respectfully urges reconsideration and withdrawal of the pending §103 rejection.

CONCLUSION

Applicant believes that the application is in condition for allowance, and an early notice to that effect is earnestly solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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